REMARKS

Favorable reconsideration of the subject application, as amended above, is respectfully requested in view of the comments below.

Claims 1-3, 6 and 8-13 are pending in the subject application. Claim 3 is cancelled herein. Accordingly, claims 1, 2, 6 and 8-13 are presented for examination on the merits.

Claim 1 has been amended to incorporate the limitations of claim 3, which is cancelled herein. As such, no new matter is added by this amendment to the claims.

I. Rejection of Claims 1-3 and 8-13 Under 35 U.S.C.§ 112, First Paragraph

Claims 1-3 and 8-13 stand rejected under 35 U.S.C. § 112 , first paragraph. The Examiner states that there is no literal support for the term "mature somatotropin" in the specification.

Applicant respectfully disagrees with the Examiner's conclusion.

The specification discloses that somatotropin is a secreted polypeptide and provides the amino acid sequence of somatotropin with the insulin secretory sequence attached (Figure 1). It further discloses that a 190 amino acid long somatotropin polypeptide was used in the present invention, the polypeptide having the sequence as shown in Figure 2. The polypeptide of Figure 2 is encoded by the nucleotide sequence shown in Figure 1 minus the secretory sequence, which is indicated by underlining. These two figures disclose the mature somatotropin in which the secretory sequence has been removed. Thus, although the term "mature somatotropin" does not appear in the specification, the skilled artisan would recognize the polypeptide in the Figures as mature somatotropin.

Moreover, it is also known in the art that somatotropin is synthesized as a precursor polypeptide of 216 amino acids, the latter 26 amino acids constituting a leader sequence that is

removed when somatotropin is released into the blood, releasing the 190 amino acid long polypeptide known as mature somatotropin. (See O'Mahoney *et al.*, of record). Thus, one of skill in the art would recognize that the somatotropin set forth in the figures and taught throughout the specification is mature somatotropin with its secretory sequence removed.

As such, the rejection of claims 1-3, 6 and 8-13 as containing new matter is improper and should be withdrawn.

II. Rejection of Claims 1, 8-11 and 13 Under 35 U.S.C. § 103(a)

Claims 1, 8-11 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentably obvious over Ballance in view of Paulson and Eskridge. The Examiner states that Ballance teaches removal of the secretory sequence and several amino acids from the amino terminal end of Growth Hormone and replacement with a yeast promoter and signal sequence. Ballance teaches that the construct is then fused downstream of an albumin construct, resulting in a recombinant Growth Hormone fusion polypeptide that can be expressed in yeast and which is more stable than naturally occurring Growth Hormone. Paulson is relied upon as teaching use of the preproinsulin secretory sequence in order to obtain a soluble secreted form of a recombinant polypeptide of interest. The Examiner relies on Eskridge as teaching identification of the sequences of preproinsulin sequence that are required to obtain secretion. The Examiner concludes, therefore, that it would have been obvious to one of ordinary skill in the art to express mature somatotropin using a heterologous signal sequence in order to achieve the desired effect of a soluble secreted Growth Hormone.

This rejection is respectfully traversed as follows.

First, the Examiner's statement concerning motivation to combine the three references is not clear. It appears that the Examiner is suggesting that the secretory sequence of the somatotropin gene does not provide a secreted, soluble protein and therefore, one of ordinary skill in the art would be motivated to replace the somatotropin secretory sequence with one that does function to secrete a soluble form of somatotropin. However, the somatotropin secretory sequence functions to provide a secreted soluble form of somatotropin. Thus, the Examiner's reasoning is unfounded. There is no motivation to remove the somatotropin secretory sequence and replace it with the insulin sequence merely to provide the expected result- secretion of a soluble protein, since with or without the replacement, somatotropin is secreted in soluble form. As such, one of ordinary skill in the art would not have been motivated to combine the cited references in the manner suggested by the Examiner.

However, even if the skilled artisan were motivated to combine the prior art, there is no teaching or suggestion in the prior art that enhanced secretion of somatotropin is achieved by replacing the somatotropin secretory sequence with the insulin secretory signal. Ballance merely teaches that

> "by fusing the hGH coding sequence to the HA coding sequence, either the 5' end or the 3' end, it is possible to secrete the fusion protein without the requirement for a yeast-driven pro sequence. This was surprising because other workers had found that a yeast derived pro sequence was needed for efficient secretion of hGH in yeast."

Page 2, § 12.

This reference teaches nothing of the effect of the secretory sequence (any secretory sequence) on secretion of the recombinant protein and does not disclose or suggest that enhanced secretion occurs as a result of replacement of the naturally occurring secretory sequence with a

heterogenous sequence. Instead, the reference teaches that fusion of HA onto hGH results in secretion from yeast cells.

Moreover, this reference does not teach that enhance secretion was achieved, as suggested by the Examiner. Instead, this reference merely teaches that some secretion is achieved in yeast, which was surprising because others had not observed any secretion in yeast unless a yeast secretory sequence is used. Thus, the primary reference teaches nothing about the effect of a heterlogous secretory sequence on secretion.

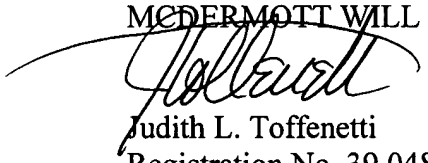
The secondary references relied on by the Examiner merely teach that heterogenous secretory sequences have been used to obtain secretion of polypeptides that are not usually secreted. These references do not disclose or suggest that **enhanced secretion** of a normally secreted polypeptide is achieved by **replacing** a naturally occurring secretory sequence with a heterogenous secretory sequence. Thus, the combination of the cited references does not disclose or suggest the claimed invention.

As can be seen from Example 1 of the specification, transfection of rat L6 cell clones with the construct of the invention containing the insulin secretory sequence ligated to the somatotropin sequence and thereby replacing the somatotropin secretory sequence, results in a secretion rate of 6 to 18 ng/ml) [Specification at page 6, lines 30-36, Table 1, page 7] In Figure 5 it is shown that pigs that have received transplanted cells transformed with the construct have enhanced levels of somatotrpin in their serum compared to control (non-transplanted) pigs. The observed enhanced secretion of somatotropin as a result of replacement of the somatotropin secretory sequence with the insulin secretory sequence as defined in the claims is surprising and is neither disclosed nor suggested in the prior art. As such, the combination of prior art fails to render the claimed invention obvious.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 500417 and please credit any excess fees to such deposit account.

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP



Judith L. Toffenetti
Registration No. 39,048

600 13th Street, N.W.
Washington, DC 20005-3096
202.756.8000 JLT:ajb:men
Facsimile: 202.756.8087
Date: October 1, 2004

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